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Gram-negative bacillary bacteremia in adults

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INTRODUCTION

Bloodstream infection is a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive care. Bacteremia due to gram-negative bacilli is a significant problem in both hospitalized and community-dwelling patients. These organisms pose serious therapeutic problems because of the increasing incidence of multidrug resistance [1]. Gram-negative bacillary sepsis with shock has a mortality rate of 12 to 38 percent; mortality varies depending, in part, on whether the patient receives timely and appropriate antibiotic therapy [2-4].

The epidemiology, microbiology, clinical manifestations, and treatment of gram-negative bacillary bacteremia will be reviewed here. The epidemiology, clinical manifestations, and treatment of infections due to specific gram-negative bacilli are discussed separately in the appropriate topic reviews.

Gram-negative bacteremia is a frequent cause of sepsis, which often must be managed prior to the receipt of microbiologic data. Antibiotic treatment in the setting of sepsis in general is discussed in detail elsewhere.

EPIDEMIOLOGY

Prevalence — Gram-negative bacilli are the cause of approximately a quarter to a half of all bloodstream infections, depending on geographic region, whether the onset of the infection is in the hospital or community, and other patient risk factors.

Hospital-onset infections — Gram-negative bacilli were once the predominant organisms associated with hospital-onset bloodstream infections in the United States [5]. Since the 1980s, gram-positive aerobes (eg, coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci), and *Candida* species have increased in relative importance. This change was especially evident in the intensive care unit (ICU) population and thought to be largely driven by device-related infections. In the United States, the National Nosocomial Infections Surveillance (NNIS) System reported that from 1986 to 2003 the proportion of bloodstream infections in ICU patients caused by gram-negative pathogens remained stable at approximately 25 to 30 percent [5]. Similarly, subsequent data from the United States National Healthcare Safety Network demonstrated that approximately a quarter of reported central line-associated bloodstream infections from 2009 to 2010 were caused by gram-negative bacilli [6].

In contrast to this stable trend, several single center studies have reported increases in the proportion of gram-negative pathogens among patients with catheter-related bacteremia. As an example, a single large United States tertiary care hospital reported a significant increase in the proportion of gram-negative bloodstream infections from 15.9 percent in 1999 to 24.1 percent in 2003 [7]. Several subsequent reports from European hospitals have shown an upward trend in the proportion of gram-negative catheter-related bloodstream infections as well [8-10]. Increasing proportions of gram-negative and yeast catheter-related bloodstream infections in these studies may be related to improved prevention efforts aimed at gram-positive central line infections, increasing antimicrobial resistance, and/or changes in surveillance practices [6,11,12]. Several of these factors are impacted by local infection prevention practices and the prevalence of drug-resistance, which may explain variable trends at individual hospitals.

Globally, the proportion of bloodstream infections caused by gram-negative bacilli differs by geographic region. As an example, data from the SENTRY Antimicrobial Surveillance Program from 1997 to 2002 demonstrated that the proportion of bacteremia caused by gram-negative bacilli was greater in Europe (43 percent) and Latin America (44 percent), than that identified in North America (35 percent) [13]. In a study from the European Antimicrobial Resistance Surveillance System, the reported frequency of bacteremia due to *Escherichia coli* increased by 8.1 percent per year from 2002 to 2008, with the additional caseload attributed to increasing antimicrobial resistance [14]. In a Brazilian multicenter study of 2563 patients with hospital-onset bacteremia, 58.5 percent of infections were due to gram-negative organisms [15].

Seasonality and the effect of warmer climates may partially explain these geographical differences. Several studies have demonstrated seasonal trends in gram-negative bacilli bacteremia in multiple continents and involving various pathogens, including *Acinetobacter*

spp, *E. coli*, *Enterobacter* spp, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [16-19]. As examples, the incidence of *P. aeruginosa* and *Acinetobacter* infections has been observed to increase by 17 percent for each 10°F (5.6°C) increase in external temperature [16]. In another study, the estimated proportion of gram-negative pathogens isolated from blood cultures in varied geographic locations demonstrated both seasonal trends and increased rates in locations closer to the equator [1]. The proportion of gross domestic product devoted to health spending was also a significant predictor, suggesting that socioeconomic factors may also play a role in the incidence of gram-negative bacteremia.

Community-onset infections — Gram-negative bacilli cause a higher proportion of community-onset than hospital-onset bacteremias, since community-onset bacteremias are more likely related to primary infections of the urinary tract, abdomen, and respiratory tract as opposed to device-related infections. In a study from two tertiary care centers in the United States, 45 percent of community-onset bloodstream infections were due to gram-negative bacilli in contrast to 31 percent of hospital-onset infections [20]. In a systematic review of studies from South and Southeast Asia that included 3506 patients with community-onset bacteremia, gram-negative organisms were the cause in 60 percent of patients [21].

Gram-negative bacteremia in community-dwelling patients frequently occurs in older populations. In a retrospective review of 238 patients older than 65 years with bacteremia, 81 percent of whom were admitted from home, a gram-negative organism was the etiologic agent in 36 percent of cases [22].

Risk factors for acquisition — Most hospitalized patients with gram-negative bacteremia have at least one comorbid condition [23,24]. In a study of 326 patients with gram-negative bacteremia, comorbid conditions were identified in 315 (97 percent) [23]. Conditions identified in this and other studies included [23-29]:

- Hematopoietic stem cell transplant [23,24]
- Liver failure [23]
- Serum albumin <3 g/dL [23]
- Solid organ transplant [23,24,28,30]
- Diabetes [23,31]
- Pulmonary disease [23,32]
- Chronic hemodialysis [26]
- HIV infection [27]
- Treatment with glucocorticoids [24]

Other host factors related to the primary source of infection may also affect the development of secondary bacteremia. As an example, one prospective study identified urinary retention and

recent urogenital surgery as host factors independently associated with the risk of bacteremia in 156 hospitalized patients with *E. coli* bacteriuria [33]. Other important procedure-related risk factors for gram-negative bacteremia include prostate biopsy and endoscopic retrograde cholangiopancreatography [34-36].

In addition to these risk factors, combat-injured military personnel and patients injured during natural disasters involving trauma in water are also at increased risk for infections caused by gram-negative bacilli [37-40].

Certain environmental gram-negative pathogens may cause hospital or medication-related outbreaks of bacteremia. As an example, a multi-state outbreak of *Serratia* bacteremia in the United States was attributed to contaminated intravenous medications from a centrally distributing pharmacy [41]. Another small, single-institution outbreak of bacteremia with *Burkholderia contaminans*, an uncommonly reported isolate, was traced to contaminated intravenous fentanyl prepared at a compounding pharmacy [42]. (See "Intravascular catheter-related infection: Epidemiology, pathogenesis, and microbiology", section on 'Infusate contamination'.)

Source of infection — Determining the source of infection is critical to therapeutic decisions, as the most likely pathogen involved, and thus appropriate empiric therapy, depends on the site of the primary infection, and varies depending on the patient population. Among critically ill patients, for example, common sources of gram-negative bacteremia include the respiratory tract and central venous catheters [43]. In contrast, several studies of older patients in the community, in nursing homes, or admitted to hospitals, have identified the urinary tract as the most frequent source of gram-negative bacteremia [44,45]. Infections of the gastrointestinal tract, biliary tract, and skin or soft tissues are less frequent sources of bloodstream infections.

MICROBIOLOGY

The frequency of specific gram-negative bacilli responsible for bacteremia differs by whether the onset of the infection is in the hospital or community and by the likely primary source of infection.

In a study of 179 cases of hospital-onset gram-negative bacillary bacteremia identified from a large database of acute care hospitals in the United States, the following distribution of pathogens was noted [46]:

- *E. coli* – 18 percent
- *K. pneumoniae* – 16 percent

- *P. aeruginosa* – 8 percent
- *Proteus* species – 1 percent
- Other gram-negative bacteria – 56 percent

Among intensive care unit (ICU) patients, the proportion of gram-negative bacteremia caused by *P. aeruginosa* is frequently higher. Patients in the ICU frequently are on or have recently been on antibiotics, which increase the risk of infections with *P. aeruginosa* and other nonfermenting gram-negative bacilli, such as *Acinetobacter* species, which have intrinsic or acquired resistance to commonly used agents. As an example, in a study that included 45 cases of hospital-onset bacteremias in an ICU in Canada, the following distribution was noted [43]:

- *P. aeruginosa* – 22.2 percent
- *Enterobacter* species – 22.2 percent
- *K. pneumoniae* – 17.8 percent
- *E. coli* – 15.6 percent
- *Serratia marcescens* – 11.1 percent

In contrast, infections with *E. coli* predominate in cases of community-onset gram-negative bacteremia, as illustrated in a study of 2796 consecutive cases of bacteremia in Italy [47]. The distribution of the approximately 570 community-onset gram-negative cases was as follows:

- *E. coli* – 76 percent
- *P. aeruginosa* – 7.9 percent
- *K. pneumoniae* – 5.4 percent
- *Proteus mirabilis* – 4.2 percent
- *Enterobacter* species – 3.7 percent

These differences reflect the observation that the urinary tract, in which *E. coli* is the most common pathogen, is the most common source for community-onset gram-negative bacteremia, whereas infections of the urinary, respiratory, and gastrointestinal tracts contribute more equally to hospital-onset bacteremia [48].

Patients who have significant health care exposures (eg, nursing home, dialysis center, recent hospitalization, or surgery) but are not in an acute care hospital at the time of infection onset can be classified separately as having health care-associated, community-onset infections. The distribution of pathogens causing bacteremia among such patients reflects a hybrid between the pure hospital- or community-onset distributions above. This is illustrated by a study of 306 cases of health care-associated, community-onset gram-negative bloodstream infections in Minnesota that demonstrated the following organism frequencies [49]:

- *E. coli* – 47.4 percent
- *K. pneumoniae* – 14.7 percent
- *P. aeruginosa* – 9.2 percent
- *Enterobacter* species – 6.5 percent
- *P. mirabilis* – 4.2 percent

Other organisms should be considered depending on the geographical region or specific epidemiologic exposures. As an example, *Salmonella* species are an important cause of community-onset bacteremia in resource-limited countries in Asia and Africa [21].

ANTIBIOTIC RESISTANCE

The treatment of gram-negative bacteremia is increasingly complicated by the rising prevalence of multidrug-resistant gram-negative bacilli strains. Normally, susceptible Enterobacterales become resistant to antimicrobial agents by acquiring resistance genes from other bacteria or through mutation and selection. Other pathogens such as *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* have inherent resistance and may acquire additional mechanisms for resistance. Multidrug-resistant pathogens and/or the genetic elements of resistance can be spread from person-to-person and bacterial species-to-species.

The burden of antimicrobial resistance among bloodstream infections caused by gram-negative organisms is substantial. As an example, among the 27,766 central-line associated bloodstream infections reported to the National Healthcare Safety Network (NHSN) in the United States between 2009 and 2010, the prevalence of resistance to broad-spectrum antibiotics was measured as follows [6]:

- *K. pneumoniae* – 29 and 13 percent resistant to third or fourth generation cephalosporins and carbapenems, respectively
- *E. coli* – 42, 19, and 2 percent resistant to fluoroquinolones, third or fourth generation cephalosporins and carbapenems, respectively
- *Enterobacter* spp – 37 percent resistant to third or fourth generation cephalosporins
- *P. aeruginosa* – 31, 26, and 26 percent resistant to fluoroquinolones, third or fourth generation cephalosporins, and carbapenems, respectively
- *A. baumannii* – 67 percent resistant to carbapenems

Additionally, there has been emergence and dissemination of extended-spectrum beta-lactamases and carbapenemases.

These multidrug-resistant pathogens are no longer limited solely to acute care hospitals. Patients are frequently infected or colonized with these pathogens in the community and in long term care facilities, and then import them into the hospital [50-53]. As an example, a single long term acute care center was the ultimate source for 60 percent of carbapenemase-producing *K. pneumoniae* infections in an outbreak that involved 40 patients in 26 facilities in the greater-Chicago area in 2009 [54].

Extended-spectrum beta-lactamases — Extended-spectrum beta-lactamases (ESBL) confer resistance to beta lactam agents. Plasmids that carry ESBLs typically carry other resistance genes as well; thus, these organisms are frequently multidrug-resistant. (See "Extended-spectrum beta-lactamases".)

Traditionally, the majority of infections with ESBL-producing organisms in the hospital are caused by *K. pneumoniae*. However, over the past decade, ESBL-producing *E. coli* has emerged as an important cause of both hospital-onset and, in particular, community-onset bacteremia. As a result, *E. coli* is now the most common cause of ESBL infection worldwide. In one series, these resistant organisms accounted for 7.3 percent of cases of community-onset bacteremia [55].

Risk factors for infection with an ESBL-producing organism among patients with bacteremia are similar to those for colonization or infection at other sites. These include admission from a nursing home, the presence of a gastrostomy tube, transplant receipt, chronic renal failure, receipt of antibiotics within the preceding 30 days, and length of hospital stay before infection [56]. (See "Extended-spectrum beta-lactamases", section on 'Risk factors'.)

Agents in the carbapenem family (imipenem, meropenem, and ertapenem) remain the drugs of choice for bacteremia caused by ESBL-producing gram-negative bacilli [57]. Treatment of infections caused by ESBL-producing organisms is discussed in more detail elsewhere. (See "Extended-spectrum beta-lactamases", section on 'Treatment options'.)

Carbapenem resistance — The widespread use of carbapenems for suspected cases of infection with ESBL-producing bacteria has contributed to the development of carbapenem resistance in many species of bacteria. The prevalence of carbapenem-resistant *K. pneumonia* increased from 1 percent in 2000 to >8 percent in 2007 [58,59]. As of September of 2012, carbapenem-resistant *K. pneumonia* had been reported in 42 states in the US [60].

Other carbapenemase classes have increased in prevalence as well. A metallo-B-lactamase, the New Delhi metallo-B-lactamase (NDM-1), was discovered in 2009 and has subsequently been identified in numerous other countries [61]. As of 2013, nine states in the US have reported cases of NDM-1 infections. Additionally, OXA-48, a Class D carbapenemase typically found in *A.*

baumannii, was described for the first time in *K. pneumoniae* in a patient in Turkey [62]. Outbreaks of infection due to this pathogen have subsequently been identified.

Overall, the most important risk factor for development of infection due to a carbapenemase-producing organism is receipt of prior antimicrobial therapy.

Treatment of serious infections, such as bacteremia, with a carbapenem-resistant organism is difficult, as such organisms often have resistance genes for other antibiotics outside the beta-lactam class, and thus effective antibiotic options are limited. A combination regimen including two or more agents is often warranted. Management of patients with infections due to carbapenemase-producing organisms should be done in consultation with an expert in the treatment of multidrug-resistant bacteria and is discussed in detail elsewhere.

CLINICAL MANIFESTATIONS

Patients with gram-negative rod bacteremia typically present with fever. Although patients can present with or without chills, the presence of shaking chills (rigors) may be an important early clinical clue that a febrile patient is bacteremic, as illustrated by a study of 396 febrile patients seen in an emergency department, of whom 60 were bacteremic (with a gram-negative organism in 42) [63]. A complaint of shaking chills (rigors) was independently associated with bloodstream infection (odds ratio [OR] 14).

Disorientation, hypotension, and respiratory failure may complicate bacteremia and are usually signs that the patient may be developing sepsis and septic shock, which is seen in approximately 25 percent of patients on presentation with gram-negative rod bacteremia [2]. Patients may rarely present with evidence of disseminated intravascular coagulation, such as petechiae and purpura, although this finding is more frequently seen in meningococcemia. (See "Definition, classification, etiology, and pathophysiology of shock in adults".)

Gram-negative bacteremia rarely occurs spontaneously without infection at another site. Thus, additional clinical manifestations will likely be present and vary by the site of the primary infection. These are discussed in further detail in the appropriate topic reviews:

- (See "Acute complicated urinary tract infection (including pyelonephritis) in adults", section on 'Clinical manifestations'.)
- (See "Acute bacterial prostatitis", section on 'Clinical manifestations'.)
- (See "Clinical evaluation and diagnostic testing for community-acquired pneumonia in adults", section on 'Clinical evaluation'.)

- (See "Clinical presentation and diagnostic evaluation of ventilator-associated pneumonia".)

- (See "Acute cholangitis: Clinical manifestations, diagnosis, and management", section on 'Clinical manifestations'.)

There are some exceptions to this rule. In patients undergoing cytotoxic chemotherapy, the resulting mucosal injury and neutropenia allow bacteria to cross mucosal membranes and enter the bloodstream despite no obvious source on clinical examination. Similarly, a splenectomized patient may present with a spontaneous bacteremia and unknown primary source. Finally, central venous catheter-related infections may present with fever and no obvious exit site infection on examination. These patients may not have an obvious primary site of infection and fever may be the only manifestation of the bacteremia. (See "Overview of neutropenic fever syndromes" and "Clinical features, evaluation, and management of fever in patients with impaired splenic function".)

DIAGNOSIS

Blood cultures — The diagnosis of gram-negative bacillary bacteremia is made when there is growth of a gram-negative bacillus on blood culture. Obtaining and interpreting blood cultures in patients suspected of having bacteremia is discussed in detail elsewhere. (See "Detection of bacteremia: Blood cultures and other diagnostic tests".)

Rapid pathogen identification — Specific molecular diagnostic tests can speed the time to identification of pathogen species and detection of resistant genetic elements from bacteria identified in blood cultures. These technologies have the potential to improve the timing of appropriate and targeted antibiotic therapy by providing identification and susceptibility information more rapidly than traditional, culture-based methods [64]. Patients with gram-negative bacteremia may specifically benefit from these rapid tests due to the wide range of possible infecting pathogens and the possibility of either intrinsic or acquired drug resistance. Due to the novelty of these tests, however, data on clinical benefit and cost-effectiveness are still emerging. Costs and microbiology laboratory expertise in molecular techniques are also seen as a barrier to their widespread use.

- Matrix-associated laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been evaluated in single center, observational studies of bloodstream infections [65-68]. Those studies of MALDI-TOF paired with antimicrobial stewardship interventions showed improvements in time to appropriate and optimal therapies [67-69], as well as some evidence of shortened hospital length of stay [68]. Patients with drug-resistant gram-negative bacillary bacteremia may experience even more clinical benefit from such testing with earlier

appropriate therapy, shortened length of stay, and 30-day mortality [70]. More recently, MALDI-TOF MS has been used for rapid identification of antimicrobial susceptibility, but this approach still needs to be refined [71].

- Multiplex polymerase chain reaction (PCR) is another emerging technology that has previously been successful in rapidly identifying gram-positive pathogens (see "Methicillin-resistant *Staphylococcus aureus* (MRSA): Microbiology and laboratory detection"). Some preliminary data describing gram-negative pathogen identification are available, although clinical experience with these tests is overall limited [72-76]. As an example, the FilmArray Blood Culture ID Panel (BCID), a rapid diagnostic that can identify 24 different bacteria, fungi, and common antimicrobial resistance genes (mecA, vanA/B, KPC) within one hour of organism growth in a blood culture bottle, was evaluated in the randomized Blood Culture Identification trial [75]. Among 617 patients whose blood cultures had positive Gram stains, use of the BCID resulted in more rapid pathogen identification compared with standard culture and susceptibility testing, and faster antibiotic de-escalation occurred when BCID was paired with real-time audit and antimicrobial stewardship feedback (compared with treatment guidance through the microbiology result). Another rapid diagnostic test, the T2Bacteria Panel, which identifies *K. pneumoniae*, *P. aeruginosa*, and *E. coli* in addition to *E. faecium* and *S. aureus*, identified these bacterial species in whole blood specimens at a mean of 3.6 to 7.7 hours (depending on the number of specimens tested) compared with 71.7 hours with standard blood cultures [76].

MANAGEMENT

Treatment of gram-negative bacillary bacteremia requires urgent and appropriate antibiotics that cover the most likely organisms, good supportive care, careful monitoring of patients, and control of the source of infection. Source control may require surgical drainage or removal of an intravascular catheter.

Antimicrobial therapy for gram-negative bacteremia can be divided into two distinct treatment phases with unique approaches: empiric therapy and directed therapy. Empiric therapy occurs when an infection is suspected but not yet confirmed. Definitive therapy occurs when the clinician has confirmed the type of infection, causative pathogen, and pathogen antimicrobial susceptibilities. New and emerging diagnostic tests are decreasing the amount of time from onset of infection to directed therapy [77].

Empiric antimicrobial therapy — Intravenous antibiotic therapy with activity against the most likely pathogens should be initiated when gram-negative bacteremia is suspected clinically or immediately following the report of positive blood culture results.

The choice of empiric antibiotics should take into account the patient's history, comorbidities, clinical syndrome, health care exposures, Gram stain data, and previous culture results in addition to local resistance patterns. Main decision points include whether to cover *P. aeruginosa* or other drug-resistant organisms and whether to use combination antimicrobial therapy. A general guideline and decision tree is provided (algorithm 1).

Algorithm for empiric antimicrobial selection for gram-negative bacillary bacteremia

Algorithm 1 - larger image below

No randomized controlled trials have evaluated empiric antibiotic regimens for gram-negative bacillary bacteremia specifically. Instead, most relevant trials are those evaluating treatment of sepsis, which includes nonbacteremic infections and bacteremia due to gram-positive or other organisms in addition to gram-negative bacillary bacteremia. As a result, treatment recommendations specifically for gram-negative bacteremia are based on somewhat indirect data from these trials in addition to retrospective or observational case series and the knowledge of the patient or hospital's prior gram-negative sensitivity data.

A retrospective study of 2731 adult patients with septic shock demonstrates the urgency of appropriate antibiotic therapy: for each hour of delay of appropriate therapy following the onset of hypotension, survival decreased by 7.6 percent [3]. The negative impact of inappropriate antibiotic therapy on survival after bloodstream infection has been demonstrated in non-ICU populations as well [78].

Suggested regimens

Patients without sepsis — For patients without signs of sepsis or septic shock (eg, no hypotension, no elevated lactate, no evidence of organ dysfunction), recommended regimens depend on the presence of immune suppression or health care exposures (algorithm 1). (See 'Indications and rationale for coverage of P. aeruginosa' below.)

- Immunocompetent patients without health care exposures can receive a broad-spectrum single agent; antipseudomonal activity is generally not necessary:
  - Third- or fourth-generation cephalosporin (ceftriaxone 2 g every 24 hours, ceftazidime 2 g every 8 hours, or cefepime 2 g every 12 hours) **OR**

- Beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam 3.375 g every six hours)

Although carbapenems are active in this setting, we typically reserve use of these broad spectrum and high-cost agents for patients who have a clear need for the additional coverage of drug-resistant organisms (eg, extended-spectrum beta lactamase [ESBL]-producing organisms).

- Patients with health care exposures or immune suppression can receive a broad-spectrum single agent with pseudomonal activity:

  - Antipseudomonal cephalosporin (ceftazidime 2 g every 8 hours or cefepime 2 g every 8 hours) **OR**

  - Beta-lactam/beta-lactamase inhibitor at antipseudomonal dosing (piperacillin-tazobactam 4.5 g every six hours) **OR**

  - Antipseudomonal carbapenem (imipenem 500 mg every six hours or meropenem 1 g every eight hours)

Empiric therapy may be further tailored based on additional history, physical examination, prior history of multidrug-resistant gram-negative pathogens, and likelihood of source of infection. As an example, for a patient with history of recurrent urinary tract infection with ESBL-producing organisms, a carbapenem would be preferable. Alternatively, for a patient with gram-negative bacteremia in the setting of cholangitis, a beta-lactam/beta-lactamase inhibitor or a carbapenem may be preferable to also cover for the possibility of anaerobic organisms.

Patients with sepsis or septic shock — For patients with sepsis or septic shock, most can be treated with appropriately dosed antipseudomonal monotherapy (algorithm 1). Since consistent achievement of therapeutic antibiotic levels and avoidance of emergent drug resistance are especially relevant for critically ill patients with gram-negative bacteremia, we favor a prolonged infusion dosing strategy for most beta-lactams for patients with septic shock, consistent with the Surviving Sepsis Guidelines recommendations to optimize pharmacodynamics and kinetics [79] (see "Prolonged infusions of beta-lactam antibiotics"). Additionally, we favor combination antimicrobial therapy in a select subset of patients who are most likely to have an infection with a drug-resistant organism and for whom inappropriate antibiotic therapy would presumably be associated with an especially high mortality (see 'Indications and rationale for coverage of P. aeruginosa' below):

- Patients who do **not** have immune suppression or risk factors for drug-resistant *P. aeruginosa* and are at hospitals where the level of resistance to the chosen empiric gram-

negative agent among the most common gram-negative pathogens does **not** exceed 10 to 20 percent can receive monotherapy with one of the following:

- Antipseudomonal cephalosporin, eg, prolonged infusion dosing of cefepime (table 1) or standard infusion dosing of cefepime (2 g every eight hours) or ceftazidime (2 g every eight hours)

  OR

- Beta-lactam/beta-lactamase inhibitor at antipseudomonal dosing, eg, piperacillin-tazobactam given as with prolonged infusion dosing (table 1) or with standard infusion dosing (4.5 g every six hours)

  OR

- Antipseudomonal carbapenem, eg, prolonged infusion dosing of imipenem or meropenem (table 1) or standard infusion dosing of imipenem (500 mg every six hours) or meropenem (1 to 2 g every eight hours, with the higher dose for more severely ill patients who have a higher risk of drug-resistant *P. aeruginosa*)

- Patients with immune suppression or risk factors for drug-resistant *P. aeruginosa* or who are at hospitals where the level of resistance to the chosen empiric gram-negative agent among the most common gram-negative pathogens exceeds 10 to 20 percent receive combination therapy with activity against *P. aeruginosa*:

  - One of the above antipseudomonal agents listed above **PLUS**

  - Tobramycin due to greater intrinsic in vitro activity compared with other aminoglycosides (see "Dosing and administration of parenteral aminoglycosides")

In patients with septic shock, additional antibiotic coverage for resistant gram-positive organisms (eg, vancomycin) is often used until cultures have been finalized.

An antipseudomonal fluoroquinolone (eg, ciprofloxacin 400 mg IV every 12 hours) is often used in combination therapy instead of an aminoglycoside. However, fluoroquinolones typically add very little additional coverage over beta-lactam antibiotics, such as antipseudomonal cephalosporins and beta-lactam/beta-lactamase inhibitor combinations, or antipseudomonal carbapenems [80]. As a result, the added benefit of using a fluoroquinolone as a second agent is questionable.

Patients with severe beta-lactam allergies — Options for empiric treatment of patients with severe beta-lactam allergies include aztreonam and fluoroquinolones. The choice

between them should take in to account the severity of infection and local rates of susceptibilities to fluoroquinolones and ceftazidime among the most common gram-negative pathogens. Susceptibility testing results for ceftazidime correlate with aztreonam susceptibilities for *P. aeruginosa* [81].

Patients with sepsis or septic shock who also have immune suppression, have risk factors for drug-resistant *P. aeruginosa*, or are at hospitals where the level of resistance to ceftazidime among the most common gram-negative pathogens exceeds 10 to 20 percent can receive combination therapy; we use combination therapy with tobramycin plus aztreonam (2 g every eight hours; if CNS infection is suspected, 2 g every six hours). Aztreonam can be used alone in patients with sepsis or septic shock and no risk factors for resistant organisms.

For patients without sepsis and without risk factors for resistant organisms, aztreonam or, if local quinolone resistance rates are <10 percent, ciprofloxacin (400 mg every 12 hours) or levofloxacin 750 mg every 24 hours, should provide adequate empiric coverage.

For patients with severe reactions to beta-lactams and prior history of drug-resistant organisms, beta-lactam desensitization should be considered.

Indications and rationale for coverage of P. aeruginosa — An important step when choosing empiric antibiotic therapy is assessing the need to adequately cover *P. aeruginosa* (algorithm 1).

For patients with hospital-onset gram-negative bacteremia, empiric therapy with activity against *P. aeruginosa* is prudent given the frequency of this pathogen among this population, especially for patients in an intensive care unit (see 'Microbiology' above). Similarly, empiric pseudomonal coverage is warranted for patients who have had recent infections with *P. aeruginosa*.

For patients with community-onset gram-negative bacteremia, the presence of health care exposures, including recent hospitalization, hemodialysis, admission from a long-term care facility, and recent intravenous antibiotics or chemotherapy, as well as immunosuppression, increase the risk of an infection with *P. aeruginosa* [49,82]. Thus, it is important for the clinician to assess for these risk factors in patients with gram-negative bacteremia; in their absence, empiric antibiotic therapy that treats *P. aeruginosa* is not likely to be beneficial.

As an example, in a study of 733 patients with community-onset bacteremia, health care exposure was associated with an increased risk of infection with *P. aeruginosa* (odds ratio [OR] 3.14, 95% CI 1.6-6.6) and fluoroquinolone-resistant organisms (OR 2.27, 95% CI 1.2-4.5) [49]. In a separate study of 303 patients with community-onset gram-negative bacteremia, severe

immunodeficiency, age >90 years, receipt of antimicrobial therapy within past 30 days, and presence of a central venous catheter or a urinary device were independently associated with *P. aeruginosa* infection [82]. For patients without any of these risk factors, the risk of *P. aeruginosa* bacteremia was 2.4 percent.

Indications and rationale for coverage of multidrug-resistant organisms — In certain infrequent situations, empiric antimicrobial coverage for multidrug-resistant organisms, such as ESBL or carbapenemase-producing Enterobacterales or *Acinetobacter*, may be warranted. These situations include cases in which the patient has a personal history of a previous infection with a multidrug-resistant gram-negative pathogen, cases of hospital-onset bacteremia in an epidemic or endemic setting in which local prevalence of such multidrug-resistant organisms is high, and cases of breakthrough gram-negative bacteremia with sepsis or septic shock in a patient already receiving antibiotic therapy for gram-negative pathogens. There are no direct data to guide when to empirically cover these multidrug-resistant organisms; we consider the circumstances listed to have the highest likelihood of involvement with a multidrug-resistant organism. In all three situations, however, we switch to an agent with a narrower spectrum that would be effective based on culture and/or susceptibility results as soon as they are available in order to avoid excessive use of broad-spectrum, high-cost, or potentially toxic agents.

For cases in which empiric coverage for carbapenemase-producing pathogens is being considered, we recommend consultation with an infectious diseases specialist to aid in selection of appropriate agents. (See "Carbapenem-resistant *E. coli*, *K. pneumoniae*, and other Enterobacterales (CRE)", section on 'Approach to treatment'.)

Treatment of multidrug-resistant organisms is discussed in detail elsewhere.

Indications and rationale for combination therapy — We favor combination antimicrobial therapy for empiric treatment of gram-negative bacteremia in patients with sepsis or septic shock when the patient is immunosuppressed (with severe neutropenia, in particular), when the patient has other risk factors for drug-resistant *P. aeruginosa* infection, or when the level of resistance to the chosen empiric gram-negative agent among the most common gram-negative pathogens in a hospital is >10 to 20 percent [2,83]. In other cases, use of a single agent is likely sufficient (algorithm 1).

The rationale for the use of two drugs is that mortality from gram-negative bacteremia is increased when patients receive inappropriate initial antimicrobial therapy and the role of a second agent may thus be to cover possible resistant pathogens when resistance rates to the primary agent are high [2,84]. In a retrospective study of 286 patients from Korea with antibiotic-resistant gram-negative bacteremia, receipt of initial inappropriate therapy was

associated with higher mortality rates than receipt of at least one antimicrobial agent to which the causative organism was susceptible (38.4 versus 27.4 percent) [2]. Similarly, in a retrospective study of 760 patients with septic shock due to gram-negative bacteremia, mortality rates were lower among patients who received appropriate compared with inappropriate empiric therapy (36 versus 52 percent) [80]. Patients who received two agents were more likely to receive appropriate therapy (78 versus 64 percent in patients who received one agent), but combination therapy was not associated with lower mortality. Of note, treatment with a fluoroquinolone provided only minimal additional coverage when added to cefepime, a carbapenem, or piperacillin-tazobactam.

This theoretical advantage of combination therapy, however, has not been supported by other studies. In a meta-analysis of 64 trials of empiric antibiotic regimens in sepsis, the addition of an aminoglycoside to a beta-lactam did not provide any mortality benefit over the beta-lactam alone but was associated with more toxicity [85]. Similarly, in a meta-analysis of two randomized trials and 15 observational studies of patients with gram-negative bacteremia, combination therapy was not associated with a decrease in mortality [86]. In a subsequent trial, 600 patients with sepsis or septic shock in 44 ICUs in Germany were randomly assigned to receive meropenem or meropenem plus moxifloxacin combination therapy [87]. Outcomes including mortality, length of hospitalization, and degree of organ failure were similar between the two groups, but patients who received combination therapy had higher rates of adverse events.

Additionally, studies evaluating the use of combination therapy for the treatment of infections due to *P. aeruginosa* have yielded conflicting results, and there remains considerable controversy surrounding the need for two versus one agent for treatment of *Pseudomonas* bacteremia. These issues are discussed in detail elsewhere. (See "Principles of antimicrobial therapy of Pseudomonas aeruginosa infections", section on 'Role of combination antimicrobial therapy'.)

Thus, since widespread use of combination antimicrobial therapy does not appear to be clinically beneficial, we do not use it routinely. Instead, we limit its use to those patients who are most likely to have drug-resistant infections and those for whom inappropriate antibiotic therapy would presumably be associated with an especially high mortality. The potential benefit for combination therapy is likely greatest in these groups. In particular, patients with immunosuppression, especially severe neutropenia, are at higher risk of mortality associated with delay in active therapy for bloodstream infections and mortality related to Pseudomonas bloodstream infection [88,89]. Bone marrow transplant recipients also suffer higher rates of drug resistance due to use of antibiotic prophylaxis and empiric therapies for neutropenic fever [90,91].

Ultimately, treating clinicians must understand local resistance patterns, evaluate the individual patient, and determine their own level of suspicion for drug-resistant gram-negative infection to justify use of combination therapy.

Directed therapy

Regimen choice — Once final culture results and antimicrobial susceptibility data are available, therapy should be tailored to the specific pathogen based upon the susceptibility results. If combination therapy was used empirically, the regimen should generally be switched to a single agent with the narrowest spectrum to which the organism is susceptible (with the exception that aminoglycosides are not typically used for monotherapy in adults) [92-94]. There is concern that routine use of broad-spectrum antibiotics for the treatment of the hospitalized patient leads to the selection of organisms resistant to those agents, as observed in the emergence of carbapenem-resistant *P. aeruginosa*, *K. pneumoniae*, and *Acinetobacter* species [95-98]. Thus, narrowing the antimicrobial spectrum based on culture results preserves the most broad-spectrum agents for treatment of multidrug-resistant pathogens.

In some cases, however, a more broadly active antibiotic is the drug of choice for directed therapy even if the organism tests susceptible to an agent with a narrower spectrum:

- **Microorganisms with extended-spectrum beta-lactamases** – For organisms that produce an ESBL, carbapenems are associated with the best outcomes [57,99]. As an example, in a randomized trial of patients with bacteremia with ceftriaxone-resistant *E. coli* or *K. pneumoniae* (most confirmed to produce an ESBL), meropenem resulted in lower mortality and adverse event rates than piperacillin-tazobactam [99]. Thus, carbapenems remain the drug class of choice, even though some of these strains may appear susceptible to cefepime, beta-lactam/beta-lactamase inhibitor combinations, or other agents. Although ertapenem is active against ESBL-producing pathogens, we agree with authors of the Infectious Disease Society of America (IDSA) antimicrobial resistance guidance and discourage its use in the setting of critical illness or hypoalbuminemia. Ertapenem is highly protein bound, its PK/PD profile suggests it may be cleared faster in such scenarios, and observational data suggested increased mortality risk as compared to meropenem [100,101]. Instead, we consider ertapenem for ESBL treatment as a step-down agent after clinical response has been assured. (See "Extended-spectrum beta-lactamases", section on 'Treatment options'.)

- ***Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella* (formerly *Enterobacter*) *aerogenes*** – These organisms have moderate to high risk of carrying inducible chromosomal AmpC beta-lactamases that are difficult to detect in many microbiology laboratories.

Cefepime retains activity against most AmpC-producing organisms except in cases where there is coproduction of ESBL, which may be predicted by cefepime MIC ≥4 [102]. Carbapenems are also highly effective for these organisms, but they should be reserved for individuals for whom cefepime is not an option because they provide unnecessarily broad coverage and are potent inducers of the Amp-C genes. For infections outside the central nervous system, use of fluoroquinolones for susceptible isolates avoids beta-lactamase induction and remains a good option due to excellent bioavailability. (See "Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects", section on 'Chromosomal beta-lactamases'.)

We agree with expert guidelines that suggest avoiding third-generation cephalosporins (eg, ceftriaxone or ceftazidime) for treatment of these organisms [102]. This recommendation is supported largely by in vitro data and observational studies in which a higher risk of clinical failure was demonstrated for bacteremia or meningitis due to *Enterobacter* species treated with third-generation cephalosporins [103-106].

Additionally, we concur with expert guidelines that suggest avoiding piperacillin-tazobactam for these organisms. In a small randomized trial (MERINO-2) of 72 individuals with gram-negative bacteremia due to inducible AmpC-producing pathogens, piperacillin-tazobactam (4.5 g every six hours) was compared with meropenem (1 g every eight hours) [59]. The results were difficult to interpret: although there was no difference in the primary outcome (a composite of death, clinical or microbiologic failure, or relapse), subgroup analysis revealed seemingly conflicting results (eg, the piperacillin-tazobactam group had higher rates of microbiologic failure but lower rates of relapse than the meropenem group). This trial and other observational and in vitro data suggest against the use of piperacillin-tazobactam for these organisms until more definitive and larger trials are performed [102].

- **Extensively resistant organisms** – Even though most infections can be treated successfully with a single agent, some infections caused by multidrug-resistant pathogens warrant a combination regimen for directed therapy and/or novel agents. As an example, for carbapenem-resistant pathogens, polymyxins such as colistin are often combined with other agents because resistance to colistin can emerge during therapy [107] (see "Carbapenem-resistant *E. coli*, *K. pneumoniae*, and other Enterobacterales (CRE)", section on 'Approach to treatment' and "Principles of antimicrobial therapy of Pseudomonas aeruginosa infections", section on 'Management of multidrug-resistant organisms'). Novel beta-lactamase-inhibitor combinations (eg, ceftazidime-avibactam) may be effective alternatives to other options for multidrug-resistant gram-negative bacilli, but their role is limited by sparse clinical data and limited availability of susceptibility testing in local laboratories [108,109]. Consultation with infectious diseases specialists is recommended when use of these agents is being

considered. (See "Combination beta-lactamase inhibitors, carbapenems, and monobactams", section on 'Beta-lactamase inhibitor combinations' and "Carbapenem-resistant *E. coli*, *K. pneumoniae*, and other Enterobacterales (CRE)", section on 'Approach to treatment'.)

When beta-lactams are used for infections with organisms that have a minimum inhibitory concentration (MIC) to the chosen antibiotic that is elevated but still within the susceptible range, we suggest a prolonged infusion of the antibiotic (table 1). (See "Prolonged infusions of beta-lactam antibiotics".)

Agents to avoid — In general, treatment of gram-negative bacteremia with tigecycline should be avoided due to low serum concentrations, emergence of resistance on therapy, and the association with an increased risk of all-cause mortality [110-113]. However, in cases of multidrug resistance, as with the production of a carbapenemase, tigecycline may be one of the only active agents, and its use may be warranted, particularly in combination with another drug.

Aminoglycosides are not typically used for monotherapy of bacteremia in adults, even if the isolate is susceptible.

Strategies to improve efficacy of definitive therapy — Several strategies can be utilized to improve the efficacy of definitive therapy against gram-negative bacteremia, including extended infusion, dose adjustment, and selective combination therapy.

Extended infusion of time-dependent antimicrobial agents increases the time over the minimal inhibitory concentration (MIC) to improve bactericidal effect of these agents. We prefer extended infusion therapy for critically ill patients, for infections in sequestered sites (eg, central nervous system), and particularly for organisms that have an elevated MIC to the agent, but that is still in the susceptible range. (See "Prolonged infusions of beta-lactam antibiotics".)

Duration and route of therapy — Duration of therapy should be determined by the clinical response of the patient in addition to the primary source and extent of infection. In most cases, the duration of antibiotic therapy is 7 to 14 days. For patients with uncomplicated Enterobacterales bacteremia who respond appropriately to antibiotic therapy (eg, no underlying endovascular, bone, joint, or CNS infection, no uncontrolled source of infection, no major immunocompromising condition, and with clinical improvement within 48 to 72 hours), we suggest a 7- rather than 14-day course [114]. Initially, antibiotics should be given parenterally, but in select patients who have defervesced and remained afebrile for 48 hours,

antibiotics may be switched to an oral agent with excellent bioavailability (eg, fluoroquinolone) if the isolate is susceptible.

For uncomplicated infections with Enterobacterales, an antibiotic duration on the shorter end of the range above is as effective as a longer course and could potentially reduce the selective pressure for antibiotic resistance [115-119]:

- In a randomized controlled trial of 604 patients hospitalized with uncomplicated gram-negative bacteremia who were afebrile and hemodynamically stable for at least 48 hours, treatment for 7 versus 14 days resulted in comparable rates of a composite endpoint that included all-cause mortality, relapse, suppurative or distant complications, readmission, or extended hospitalization at 90 days (46 versus 48 percent; risk difference -2.6 percent, 95% CI -10.5 to 5.3 percent) [115]. Mortality rates at 14 and 28 days were also not statistically different between the two groups (2.3 and 5 versus 1.3 and 4.4 percent). The majority of patients had a urinary source (68 percent) and Enterobacterales infection (90 percent); 18 percent had multidrug-resistant pathogens as their incident infections. New resistant infections developed in approximately 10 percent of patients in each group.

- In a randomized trial of over 3600 hospitalized patients with bloodstream infections caused by gram-negative or gram-positive bacteria, 90-day mortality was similar in patients treated with seven days of antibiotics (15 percent) compared with 14 days of therapy (16 percent) [117]. Over half of patients were in the intensive care unit, and the most common sources of infection were the urinary tract, abdomen, and lung. Patients with immunocompromise, prosthetic heart valves or vascular grafts, a syndrome (eg, endocarditis) requiring prolonged therapy, or *Staphylococcus aureus* bacteremia were excluded from the study. A separate analysis of the study population found no difference in development of resistant pathogens between the two study groups [118].

- A meta-analysis of four randomized trials (including the two described above) found no difference in 90-day mortality for patients treated with seven days of antibiotics (12.8 percent mortality) compared with 14 days (13.7 percent; RR for death 0.91, 95% CI 0.69-1.22) [119].

We do not routinely use C-reactive protein (CRP) to guide antibiotic duration; it is uncertain whether this is a useful tool. In a randomized trial including more than 500 adults with uncomplicated gram-negative bacteremia, patients were randomly assigned to receive antibiotic treatment duration guided by CRP (with antibiotic discontinuation once CRP declined by 75 percent), a fixed 7-day treatment duration, or a fixed 14-day treatment duration; 30-day clinical failure rates were 2.4, 6.6, and 5.5 percent, respectively [120]. CRP-guided treatment and 7-day treatment were noninferior to 14-day treatment (difference in CRP versus 14-day

treatment -3.1 percent [1-sided 97.5% CI -∞ to 1.1]; difference in 7-day versus 14-day group 1.1 percent [1-sided 97.5% CI −∞ to 6.3]). However, the authors note that interpretation of these findings is limited by the low event rate and large noninferiority margin, as well as low adherence to the CRP strategy with broad range of treatment duration in this group.

Data also support a switch to oral agents in select cases [121-123]. In a large propensity-matched, retrospective cohort study of patients with uncomplicated Enterobacterales bacteremia, switching to an oral antibiotic regimen within five days of initiating a parenteral regimen was associated with similar 30-day mortality and recurrence rates as continuing parenteral therapy for the duration of the course [121]. Of note, the majority of patients received either a quinolone or trimethoprim-sulfamethoxazole and had urinary infections and secondary bacteremia. The study was too small to detect a difference in outcomes among those who received agents with low versus high bioavailability. In a meta-analysis of observational studies, transition to an oral beta-lactam (which is considered a low bioavailability drug class) was associated with a higher rate of recurrent infection compared with transition to an oral fluoroquinolone; however, the beta-lactam doses used were potentially suboptimal [122]. Thus, the efficacy of low bioavailability oral agents (when adequately dosed) for treatment of gram-negative bacteremia is not yet established.

Control of the source of infection — In addition to antibiotic therapy, management of gram-negative bacteremia requires the identification of the source of infection and resolution of infection at the source. This includes removing catheters in catheter-related bloodstream infections and drainage of abscesses.

Catheter removal — Catheter-related gram-negative bacteremia often requires removal of the catheter to prevent relapse of infection. Long-term catheters should be removed in the setting of septic shock, suppurative thrombophlebitis, endocarditis, bacteremia that continues despite >72 hours of appropriate antimicrobial therapy, or infection due to *P. aeruginosa* [124]. Otherwise, line salvage can be attempted in the setting of uncomplicated catheter-related bacteremia due to gram-negative pathogens (other than *P. aeruginosa*) with 10 to 14 days of systemic therapy coupled with antibiotic lock therapy. (See "Lock therapy for treatment and prevention of intravascular non-hemodialysis catheter-related infection" and "Intravascular non-hemodialysis catheter-related infection: Treatment".)

Supportive care — In addition to urgent treatment with antibiotics, patients with sepsis must be treated quickly with fluids and other supportive care [125]. Patients with septic shock should be managed in an intensive care unit. (See "Evaluation and management of suspected sepsis and septic shock in adults".)

Follow-up blood cultures — For patients who clinically improve after the initiation of appropriate antibiotic therapy, repeat blood cultures to document clearance of bacteremia may be unnecessary [114]. Persistent bacteremia is uncommon with gram-negative pathogens, even in immunocompromised individuals, as long as the source of infection has been controlled [126].

In a retrospective study of bacteremia cases in which blood cultures were repeated, persistent bacteremia was observed in only 6 percent of the 140 gram-negative bacilli cases compared with 21 percent of the 206 gram-positive cocci cases [127]. Fever at the time of repeat blood culture was associated with persistent gram-negative bacteremia (seen in six of the eight persistent cases).

Repeat blood cultures at 48 hours after the positive set to document clearance are warranted for patients who continue to be febrile or otherwise acutely ill (or relapse) despite antibiotic therapy or for those in whom source control has not been assured. Specific risk factors for persistent gram-negative bacteremia in observational studies include the following [128]:

- End-stage renal disease on hemodialysis
- Presence of a central venous catheter
- Infection due to an extended-spectrum beta-lactamase (ESBL)-producing pathogen
- Resistance to initial antibiotic treatment
- Unfavorable clinical response at 48 hours
- Serratia species infection [129]

PROGNOSIS

The reported mortality rate of patients with gram-negative bacteremia ranges from 12 to 38 percent [2,4,130-132]. In a retrospective study of 81 episodes of gram-negative bacteremia in nonneutropenic patients from Greece, factors associated with a higher death rate included [4]:

- Acute respiratory distress syndrome (ARDS)
- Septic shock
- Disseminated intravascular coagulation (DIC)
- Anuria
- Presence of a central venous catheter
- Unknown origin of infection
- Inappropriate antibiotic treatment

In this study, early initiation of appropriate antibiotic therapy was the most important intervention that favorably affected the outcome.

Impact of antibiotic resistance — Antibiotic resistance among gram-negative bacteria is generally believed to increase mortality. However, it is often difficult to measure the impact of the presence of antibiotic resistance itself because of differences in underlying illnesses (host related issues) and source of infection between patients with resistant and susceptible infections, the variable timing and receipt of appropriate therapy, and methodologic problems of some studies.

The following findings illustrate this difficulty:

- A retrospective case-control study of bacteremia due to gram-negative bacilli in neutropenic cancer patients found that attributable mortality was similar in patients with gram-negative bacteremia whether they were infected with susceptible or multiresistant strains (15.7 versus 13.8 percent) [133]. In contrast, in a subsequent study of patients with bacteremia on a hematologic ward, bacteremia caused by multidrug-resistant *P. aeruginosa* was associated with a higher mortality compared with other gram-negative pathogens and susceptible *P. aeruginosa* (36 versus 11 and 27 percent, respectively) [134].

- Excess mortality associated with resistant gram-negative infections may be a result of inappropriate empiric therapy (eg, treatment with an antibiotic that does not have activity against the causative organism due to inherent or acquired antibiotic resistance). In a series of 286 cases of antibiotic-resistant gram-negative bacteremia, higher mortality was associated with receipt of inappropriate compared with appropriate empiric therapy (30 day mortality 38 versus 27 percent) [2]. Similarly, a prospective cohort analysis of 535 patients with sepsis due to *P. aeruginosa*, *Acinetobacter* species, or Enterobacterales demonstrated that initial treatment with a regimen against which the organism was resistant was associated with higher mortality (adjusted OR 2.28, 95% CI 1.69-3.08; p = 0.006) [135].

- A retrospective study of 301 patients with bacteremia due to multidrug-resistant gram-negative pathogens failed to demonstrate that multidrug-resistance was associated with increased mortality, but it was associated with increased length of hospitalization by six days compared with patients with infections due to susceptible pathogens (p<0.001) [136].

INFORMATION FOR PATIENTS

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sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

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- Basics topics (see "Patient education: Sepsis in adults (The Basics)" and "Patient education: Multidrug-resistant organisms (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Gram-negative bacilli cause up to half of all bloodstream infections. (See 'Epidemiology' above.)

  The spectrum of bacteria differs depending on prior health care exposures and the anatomic source of infection. For example, *Pseudomonas aeruginosa* frequently causes hospital-onset infections whereas most community-acquired infections are due to *Escherichia coli* from urinary tract infections. (See 'Microbiology' above and 'Source of infection' above.)

  Multidrug-resistant strains are increasingly common causes of gram-negative bacteremias. Such pathogens are no longer limited to hospitals and often infect individuals in the community who have significant health care exposures or live in long-term care facilities. (See 'Antibiotic resistance' above.)

- **Clinical manifestations** – Fever is typical, and rigors can be indicative of bacteremia. Septic shock is seen in approximately 25 percent of patients on presentation and may be preceded by disorientation and respiratory failure. (See 'Clinical manifestations' above.)

  Focal symptoms vary based on the primary site of infection. However, patients with neutropenia or catheter-related bloodstream infections often have no focal symptoms. (See 'Clinical manifestations' above.)

- **Diagnosis and diagnostic evaluation** – Diagnosis is based on growth of a gram-negative bacillus on blood culture. (See 'Diagnosis' above.)

  Obtaining blood cultures is important when bacteremia is suspected. Obtaining and interpreting blood cultures in this setting is discussed in detail elsewhere. (See "Detection of bacteremia: Blood cultures and other diagnostic tests".)

- **General management** – Management includes urgent empiric antibiotics, supportive care, careful monitoring, and control of the source of infection, which may require surgical drainage or removal of an intravascular catheter. (See 'Management' above.)

- **Empiric antibiotic selection** – The choice of empiric antibiotics should consider the patient's history, recent antimicrobial exposure, comorbidities, clinical syndrome, prior health care exposures, Gram stain data, and previous culture results. Other important therapeutic decisions include whether to empirically cover *P. aeruginosa* or other multidrug-resistant organisms and when to employ combination antimicrobial therapy (algorithm 1). (See 'Empiric antimicrobial therapy' above.)

  - **Patients without sepsis or septic shock** – Regimen selection is based on whether anti-pseudomonal coverage is indicated (eg, prior health care exposure or immunosuppression). Example regimens are listed in the text. (See 'Patients without sepsis' above and 'Indications and rationale for coverage of P. aeruginosa' above.)

    - **Immunocompetent patients without health care exposures** – We recommend a single broad-spectrum antibiotic (**Grade 1B**). Antipseudomonal activity is generally not necessary.

    - **Patients with immunosuppression or health care exposures** – We recommend a single broad-spectrum antibiotic with antipseudomonal activity (**Grade 1B**).

  - **Patients with sepsis or septic shock** – We favor combination antimicrobial therapy. Although there are no direct data demonstrating benefit of combination therapy, use of two agents increases the likelihood that empiric therapy will be effective against the infecting organism. Example regimens are listed in the text. (See 'Patients with sepsis or septic shock' above and 'Indications and rationale for combination therapy' above.)

    - **Patients who are immunosuppressed, have risk factors for *P. aeruginosa*, or are at hospitals where the rate of resistance to the chosen empiric gram-negative agent exceeds 10 to 20 percent** – For these individuals, we suggest empiric therapy with a combination of two antipseudomonal agents (**Grade 2C**).

    - **Patients without any risk factors for resistant organisms** – For these individuals, we recommend treatment with a single antipseudomonal agent (**Grade 1B**).

  - **Narrowing therapy** – Once culture and susceptibility data are available, we typically narrow coverage to target the pathogen. Exceptions include pathogens with extended-spectrum beta-lactamase (ESBL) production or moderate to high risk of inducible AmpC resistance. (See 'Directed therapy' above.)

- **Duration of antibiotic therapy** – The total duration of therapy is usually 7 to 14 days. For patients with uncomplicated bacteremia due to Enterobacterales who have source control and appropriate response to therapy, we suggest a 7- rather than 14-day course (**Grade 2B**). Although initial therapy is parenteral, oral agents with high bioavailability can be used to complete therapy after clinical improvement, if susceptibilities allow. (See 'Duration and route of therapy' above.)

- **Mortality** – Reported mortality rates range from 12 to 38 percent and are even higher among those who also have sepsis. Infection with drug-resistant organisms is associated with greater mortality. (See 'Prognosis' above.)

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Topic 3149 Version 58.0

GRAPHICS

Algorithm 1: **Algorithm for empiric antimicrobial selection for gram-negative bacillary bacteremia**

This is an algorithm titled Algorithm for empiric antimicrobial selection for gram-negative bacillary bacteremia. Legend: This algorithm reflects a general approach to the empiric selection of antibiotic therapy for gram-negative bacillary bacteremia. Patients with a history of infection with extremely drug-resistant organisms (such as carbapenem-resistant Enterobacteriaceae) warrant additional consideration and consultation with an expert in infectious diseases. Listed doses are for parenteral administration in adults with normal renal function.

This algorithm reflects a general approach to the empiric selection of antibiotic therapy for gram-negative bacillary bacteremia. Patients with a history of infection with extremely drug-resistant organisms (such as carbapenem-resistant Enterobacteriaceae) warrant additional consideration and consultation with an expert in infectious diseases. Listed doses are for parenteral administration in adults with normal renal function.

ESBL: extended-spectrum beta-lactamases.

* Immunocompromising conditions include: poorly controlled diabetes mellitus, chronic high-dose corticosteroid use, use of other immunosuppressive agents, neutropenia, advanced HIV infection, B or T leukocyte deficiency.

¶ Health care exposures include: hospitalization, hemodialysis, residence in a long-term care facility, and intravenous antibiotic use or chemotherapy.

Δ Empiric therapy should be further tailored based on additional history, prior history of multidrug-resistant gram-negative pathogens, and likely source of infection. As an example, a carbapenem (imipenem or meropenem) is preferable for a patient with a history of infection with ESBL-producing organisms within the prior 6 months. Alternatively, for a patient with gram-negative bacteremia in the setting of cholangitis, a beta-lactam/beta-lactamase inhibitor or a carbapenem may be preferable to provide anaerobic coverage. For patients with sepsis or septic shock, broad-spectrum gram-positive coverage is often also used until cultures have been finalized. Drug dose lists are for adult patients with normal renal function. Refer to other UpToDate content for options for patients with severe beta-lactam allergies.

◇ For patients with gram-negative bacillary bacteremia and septic shock, we favor a prolonged infusion dosing strategy for most beta-lactams. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

§ When there is a risk, we favor tobramycin over gentamicin or amikacin because tobramycin has greater intrinsic in vitro activity. Tobramycin dosing depends on the patient's weight and creatinine clearance. Dosing adjustments should be based on the results of serum drug concentration monitoring. Refer to other UpToDate content on aminoglycoside dosing.

Graphic 89418 Version 8.0

[1-8]

Table 1: **Dosing for prolonged infusions of beta-lactams**

	Creatinine clearance	Dose	Dosing interval	Infusion time
Piperacillin-tazobactam*	>20 mL/minute	3.375 or 4.5 g	Every 8 hours	4 hours
	≤20 mL/minute or intermittent HD or PD	3.375 or 4.5 g	Every 12 hours	4 hours
	CRRT¶	3.375 or 4.5 g	Every 8 hours	4 hours
Cefepime△	≥50 mL/minute	2 g	Every 8 hours	3 to 4 hours
	30 to 49 mL/minute	2 g	Every 12 hours	3 to 4 hours
	15 to 29 mL/minute	1 g	Every 12 hours	3 to 4 hours
	<15 mL/minute or intermittent HD	1 g	Every 24 hours	3 to 4 hours
	CRRT¶	2 g	Every 12 hours	3 to 4 hours
Imipenem◇	>70 mL/minute	500 mg or 1 g	Every 6 hours	3 hours
	41 to 70 mL/minute	500 mg or 750 mg	Every 8 hours	3 hours
	21 to 40 mL/minute	250 or 500 mg	Every 6 hours	3 hours
	6 to 20 mL/minute or intermittent HD or PD	250 or 500 mg	Every 12 hours	3 hours
	CRRT¶	500 mg	Every 6 hours	3 hours
Meropenem§	≥50 mL/minute	1 or 2 g	Every 8 hours	3 hours
	25 to 49 mL/minute	1 or 2 g	Every 12 hours	3 hours
	10 to 24 mL/minute	500 mg or 1 g	Every 12 hours	3 hours
	<10 mL/minute or intermittent HD	500 mg or 1 g	Every 24 hours, given after HD	3 hours
	CRRT¶	1 or 2 g	Every 12 hours	3 hours
Ampicillin-sulbactam¥	≥30 mL/minute	9 g	Every 8 hours	4 hours
	15 to 29 mL/min	6 g	Every 8 hours	4 hours

	<15 mL/min or intermittent HD	6 g	Every 12 hours	4 hours
	CRRT[¶]	9 g	Every 8 hours	4 hours
Ceftazidime-avibactam[‡]	>50 mL/minute	2.5 g	Every 8 hours	2 to 3 hours
	31 to 50 mL/minute	1.25 g	Every 8 hours	2 to 3 hours
	16 to 30 mL/minute	0.94 g	Every 12 hours	2 to 3 hours
	6 to 15 mL/minute	0.94 g	Every 24 hours	2 to 3 hours
	≤5 mL/minute or intermittent HD	0.94 g	Every 48 hours, given after HD	2 to 3 hours
	CRRT[¶]	1.25 g	Every 8 hours	2 to 3 hours
Ceftolozane-tazobactam	>50 mL/minute	3 g	Every 8 hours	3 hours
	30 to 50 mL/minute	750 mg or 1.5 g	Every 8 hours	3 hours
	15 to 29 mL/minute	375 or 750 mg	Every 8 hours	3 hours
	<15 mL/minute or intermittent HD	150 or 450 mg	Every 8 hours (start after loading dose)	3 hours
	CRRT[¶]	750 mg or 1.5 g	Every 8 hours	3 hours
Cefiderocol	≥120 mL/min	2 g	Every 6 hours	3 hours
	60 to 119 mL/minute	2 g	Every 8 hours	3 hours
	30 to 59 mL/minute	1.5 g	Every 8 hours	3 hours
	15 to 29 mL/minute	1 g	Every 8 hours	3 hours
	<15 mL/minute or intermittent HD	750 mg	Every 12 hours	3 hours
	CRRT[¶]	1.5 g	Every 12 hours	3 hours
Aztreonam[†] (in combination with ceftazidime-avibactam)	≥30 mL/min	2 g	Every 6 to 8 hours	3 hours
	10 to 29 mL/min	1 g	Every 6 to 8 hours	3 hours
	<10 mL/min or intermittent HD	2 g	Every 24 hours	3 hours
	CRRT[¶]	2 g	Every 12 hours	3 hours

	Estimated glomerular filtration rate	Dose	Dosing interval	Infusion time
Meropenem-vaborbactam	≥50 mL/minute	4 g	Every 8 hours	3 hours
	30 to 49 mL/minute	2 g	Every 8 hours	3 hours
	15 to 29 mL/minute	2 g	Every 12 hours	3 hours
	<15 mL/minute or intermittent HD	1 g	Every 12 hours	3 hours
	CRRT¶	2 g	Every 8 hours	3 hours

The dosing recommendations reflect the opinion of UpToDate authors for adult patients with adequate intravenous access. The dosing strategies outlined may not be appropriate for all practice settings; they are based on pharmacodynamic models that use MIC distribution assumptions that may not match local patterns. Indications for use of extended infusions of beta-lactams are discussed in the dedicated topic on this issue. Separate calculators for estimation of creatinine clearance or glomerular filtration rate in conventional or International System of Units are available within UpToDate.

CRRT: continuous renal replacement therapy; CVVHDF: continuous venovenous hemodiafiltration; HD: hemodialysis; MIC: minimum inhibitory concentration; PD: peritoneal dialysis.

* The higher dose of piperacillin-tazobactam (4.5 g) is used in certain situations, such as expected augmented drug clearance (as with critical illness or cystic fibrosis) or in cases of infections with pathogens that have high, but still susceptible, MICs to piperacillin-tazobactam when alternative agents are not appropriate. This higher dose can also be used for empiric treatment in communities or institutions where the *P. aeruginosa* MICs to piperacillin-tazobactam range higher than 32. Some studies have also used a dose of 4.5 g every 6 hours infused over 3 hours.

¶ The recommendations for CRRT dosing are based off of CVVHDF with a flow rate of 1 liter per hour and minimal residual renal function.

Δ Some studies have also used a 3-hour infusion time for cefepime.

◇ Imipenem is dosed by both weight and renal function. Dosing above is based on patient weight >70 kg.

§ The higher dose of meropenem is used in patients with infections of the central nervous system or other life-threatening infections such as necrotizing fasciitis.

¥ High dosing of the sulbactam component with extended infusion times is recommended for carbapenem-resistant *Acinetobacter* infections[9]. Note that for patients with normal kidney function, an alternative dosing strategy is 27 g IV as a continuous infusion over 24 hours for patients with normal renal function.

‡ Some experts prefer a 3-hour extended infusion time (instead of standard 2 hours) for ceftazidime-avibactam for infections caused by carbapenem-resistant Enterobacterales, difficult-to-treat *P. aeruginosa*, and *S. maltophilia*.

† Extended infusion aztreonam is preferred when used in combination with ceftazidime-avibactam for treatment of multidrug-resistant pathogens (eg, carbapenem-resistant Enterobacterales or *Stenotrophomonas*). In these cases, it is preferred that both agents are administered at the same time over 3 hours. Note the guideline panel suggests dosing aztreonam every 6 hours of aztreonam, but clinical data are lacking. Dosing every 8 hours is also reasonable and is logistically simpler, especially if clinical stability has been achieved[9-12].

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